Neonatal hematological and biochemical complications in TTTS and TAPS

Verbeek, L.I.

Chapter 7
Short-term postnatal renal function in twin anemia-polycythemia sequence

Lianne Verbeek
Femke Slaghekke
Romain Favre
Marine Vieujoz
Francesco Cavigioli
Gianluca Lista
Dick Oepkes
Enrico Lopriore

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Abstract

Objective: To evaluate the short-term renal function in neonates with twin anemia-polycythemia sequence (TAPS).

Methods: All consecutive monochorionic twins with TAPS with double survivors admitted to three European centers were included in this retrospective study. Each twin pair was matched for gestational age at birth with a control twin pair unaffected by TAPS or twin-twin transfusion syndrome. Creatinine and urea levels in the first week after birth were recorded. Short-term postnatal renal dysfunction was defined as creatinine >100 μmol/l during the first week after birth.

Results: A total of 52 TAPS twin pairs and 52 control twin pairs with a median gestational age of 31 weeks at birth were included in the study. In the TAPS group, donors had higher mean creatinine levels compared to recipients, 85 versus 71 μmol/l, respectively ($p = 0.001$). Short-term renal dysfunction was detected in 26.0% (13/50) of the donors versus 6.3% (3/48) of the recipients ($p = 0.022$). In the control group, no inter-twin differences in creatinine levels were found.

Conclusions: Donor twins with TAPS have higher creatinine levels than recipient twins, suggesting that chronic inter-twin transfusion in TAPS may also cause short-term renal dysfunction. Long-term renal consequences in TAPS donors require further investigation.

Introduction

Twin anemia-polycythemia sequence (TAPS) is a recently described disorder, which is characterized by large inter-twin hemoglobin differences without signs of twin oligo-polyhydramnios sequence [1]. TAPS can be detected in 2-16% of the twin-twin transfusion syndrome (TTTS) pregnancies treated with laser surgery (post-laser TAPS) [1,2,3,4] and can also occur spontaneously in about 3-5% of the monochorionic twin pregnancies (spontaneous TAPS) [5]. The pathophysiology of TAPS is based on the presence of few minuscule arteriovenous placental anastomoses allowing slow but chronic inter-twin blood transfusion, resulting in chronic anemia (with reticulocytosis) in donors and polycythemia in recipients [1].

In TTTS, various renal complications have been reported in donor twins, including renal cortical necrosis and fibrosis, transient renal insufficiency, acute renal failure requiring long-term peritoneal dialysis or permanent tubular dysfunction with polyuria due to renal dysgenesis [6]. In TAPS, knowledge on biochemical differences between donors and recipients is sparse. Recent studies have shown that donors in TAPS have lower albumin and total protein levels due to chronic blood transfusion into the circulation of the recipient, causing loss of nutrients [7]. Whether chronic blood loss in TAPS donors may also cause renal impairment is not known. The aim of this retrospective study is to evaluate the short-term renal function in donors and recipients with TAPS, compared to a control group of uncomplicated monochorionic twins matched for gestational age at birth.

Patients and Methods

We performed a retrospective analysis of all consecutive monochorionic twin pairs with TAPS admitted between August 2003 and December 2014 to the neonatal intensive care unit of three European tertiary care centers: the Leiden University Medical Center (The Netherlands), Strasbourg Teaching Hospital (France) and V. Buzzi Children Hospital, Milan (Italy). The three centers are tertiary care centers managing all types of complications of monochorionic pregnancies and serve as regional and national referral centers for fetoscopic laser treatment for TTTS or TAPS. TAPS was diagnosed using previously reported antenatal and/or postnatal criteria. Antenatal criteria included an increased peak systolic velocity in the middle cerebral artery >1.5 multiples of the median in the donor twin, and a reduced peak systolic velocity in the middle cerebral artery (<1.0 multiples of the median) in the recipient twin, in the absence of oligo-polyhydramnios sequence. Postnatal criteria included an inter-twin hemoglobin (Hb) difference >8.0 g/dl and at least one of the following: reticulocyte count ratio >1.7 or a placenta with only small (diameter <1 mm) placental vascular anastomoses [4].

To compensate for the lack of data on normal creatinine levels per gestational age, a control group was incorporated in the study design. Each twin pair with TAPS was compared with an uncomplicated monochorionic twin pair unaffected by TAPS or TTTS. The control pregnancies were the next uncomplicated twin pregnancy delivered at a matched gestational age (±1 week of gestation). All neonates of the control group were born at the Leiden University Medical Center. Since the vast majority of donor twins with TAPS are smaller than recipients [8], we compared the data in the control twin pairs between the smaller twin and the larger twin. We excluded all twin pregnancies with single or double intrauterine death, TAPS cases treated with fetoscopic laser surgery and cases with congenital urinary tract anomalies.

At birth, the following neonatal parameters were routinely measured and recorded in all twins: blood pressure, heart rate, Hb levels and reticulocyte count. Blood pressure was recorded noninvasively. Creatinine and urea levels were routinely measured in the first week after birth. We excluded creatinine and urea levels measured within 48 h after birth to reduce the maternal influence on creatinine and urea levels in the neonates. When multiple values were measured, we included the highest values. We also compared the creatinine and urea levels between the subgroups with spontaneous TAPS cases and post-laser TAPS cases. Creatinine measurement was performed using an enzymatic method (Roche Modular P800).

We recorded the urine output (in ml/kg/h) during the first 3 days after birth. Short-term postnatal renal dysfunction was defined as creatinine >100 μmol/l during the first week after birth.

The following perinatal variables were recorded: gender, gestational age at birth, birth weight, birth weight discordance, asphyxia, patent ductus arteriosus and neonatal mortality. Birth weight discordance was assessed and calculated as follows: [(birth weight larger twin - birth weight smaller twin)/birth weight larger twin] × 100. Asphyxia was defined as the presence of at least three of the following criteria: decelerative cardiotocogram, an arterial umbilical cord pH level <7.10, a 5-min Apgar score <5, spontaneous breathing >5 min after birth or multi-organ failure. Neonatal mortality was defined as death within 28 days after birth.

Statistics

Data were reported as means and standard deviations (SD). We calculated that a minimum of 42 TAPS twin pairs were required to demonstrate a difference in creatinine levels of 10 μmol/l with an SD of 20 μmol/l between donors and recipients, with a significance of 0.05 and a power of 80%, by two-tailed analysis. The results of the continuous variables within twin pairs were analyzed using the related-samples Wilcoxon signed-rank test. The Mann-Whitney U test was used to compare the continuous variables between the TAPS group and the control group. For analyses of paired nominal variables, the McNemar test was used. For statistical analyses, two-sided tests were employed, and a p value of <0.05 was considered to indicate statistical significance. Analysis was performed using SPSS version 17 (SPSS, Inc., Chicago, Ill., USA).

Results

A total of 52 TAPS twin pairs fulfilled the inclusion criteria, of which 39 (75%) were born in Leiden, 10 (19%) in Strasbourg and 3 (6%) in Milan. The characteristics of the included patients in the TAPS group and control group of uncomplicated MC twins are summarized in table 1. Of the 52 TAPS twin pairs, 18 (35%) pairs were spontaneous TAPS cases and 34 (65%) were post-laser TAPS cases.

TABLE 1 Baseline characteristics in study group with TAPS and control group

	TAPS group N[a] = 104	Control group N[a] = 104	P-value
Cesarean delivery – no. (%)	70 (67.3%)	45 (43.3%)	0.001
Female – no. (%)	50 (48.1%)	48 (46.2%)	0.782
Gestational age at birth - wk[b]	31 ± 2	31 ± 3	0.584
Birth weight difference - %[c]	15.9 ± 12.0	13.4 ± 13.3	0.127

[a]Refers to the number of neonates
[b]Value given as mean ± SD
[c]Birth weight difference was calculated as follows: ((birth weight larger twin – birth weight smaller twin)/ birth weight larger twin) x 100

Table 2 shows the hematological and biochemical differences at birth between donors and recipients (TAPS group) and the control group. In the TAPS group, creatinine and urea levels from the donor and recipient were measured on the same day in 63% of the cases. In 10% of the cases, there was a 1-day difference between the two measurements, in 14% a 2-day difference and in 12% a 3-day difference. In the control group, creatinine and urea levels were measured on the same day in both neonates in 68%, with a 1-day difference in 20%, a 2-day difference in 8% and a 3-day difference in 4%. Donor twins had significantly higher creatinine levels during the first week after birth compared to recipients in the TAPS group, 85 and 71 µmol/l, respectively (p = 0.001). Short-term renal dysfunction (a creatinine level >100 µmol/l) was detected in 26.0% (13/50) of the donors versus 6.3% (3/48) of the recipients (p = 0.022). None of the TAPS donors had evidence of severe renal damage of renal failure requiring treatment during the neonatal period. In the control group, no inter-twin differences in creatinine were found (table 2). Renal dysfunction was detected in 3 (5.9%) of the smaller twins and in 5 (9.8%) of the larger twins.

TABLE 2 Hematological and biochemical differences at birth between donors and recipients (TAPS group) and smaller and larger twins (control group)

	TAPS group			Control group		
	Donors (N = 52)	Recipients (N = 52)	p-value	Smaller twins (N = 52)	Larger twins (N = 52)	p-value
Hemoglobin – g/dL[a]	8.8 ± 2.8	21.6 ± 3.1	0.000	16.4 ± 3.1	16.0 ± 2.6	0.289
Reticulocyte count –promille[a]	138 ± 85[b]	51 ± 48[c]	0.000	68 ± 20[d]	68 ± 22[e]	0.228
Inter-twin hemoglobin difference – g/dL[a]	12.8 ± 4.2			2.3 ± 2.0		0.000
Inter-twin reticulocyte count - promille[a]	91 ± 59[b]			10 ± 28[d]		0.000
Creatinine week 1 - µmol/l[a]	85 ± 27[f]	71 ± 17[b]	0.001	76 ± 15[g]	78 ± 24[g]	0.727
Day after birth creatinine measured[a]	3.8 ± 1.8[f]	3.4 ± 1.5[b]	0.109	3.1 ± 1.9[g]	3.3 ± 1.3[f]	0.263
Creatinine >100 µmol/l[a] – no. (%)	13 (26.0%)[f]	3 (6.3%)[b]	0.022	3 (5.9%)[g]	5 (9.8%)[g]	0.687
Urea week 1 – mmol/l[a]	6.0 ± 3.5[f]	5.9 ± 3.4[b]	0.548	5.0 ± 2,2[g]	5.8 ± 2,4[g]	0.007
Day after birth urea measured[a]	3.8 ± 1.7[f]	3.5 ± 1.6[b]	0.553	3.3 ± 1.3[g]	3.1 ± 1.9[f]	0.263
Inter-twin creatinine difference - µmol/l[a]	20 ± 22[b]			13 ± 22[c]		0.007
Inter-twin urea difference - mmol/l[a]	2.1 ± 2.0[b]			2.1 ± 2.9[c]		0.665

[a]Value given as mean ± SD.

[b]Assessed in 48/52 twin pairs. [c]Assessed in 49/52 neonates. [d]Assessed in 39/52 twin pairs. [e]Assessed in 40/52 twin pairs. [f]Assessed in 50/52 twin pairs. [g]Assessed in 51/52 neonates.

Analyses regarding creatinine and urea levels between the spontaneous TAPS group and the post-laser TAPS group are shown in table 3. Differences between donors and recipients appeared to be slightly more prominent in the spontaneous TAPS group.

TABLE 3 Biochemical differences at birth between donors and recipients in the spontaneous TAPS group and in the post-laser TAPS group

	Spontaneous TAPS			Post-laser TAPS		
	Donors (N=18)	**Recipients (N=18)**	**p-value**	**Donors (N=34)**	**Recipients (N=34)**	**p-value**
Creatinine week 1 - µmol/l[a]	88 ± 27[b]	70 ± 17[b]	0.006	84 ± 28[c]	73 ± 18[c]	0.051
Day after birth creatinine measured[a]	3.8 ± 1.8[b]	3.1 ± 1.5[b]	0.121	3.8 ± 1.9[c]	3.5 ± 1.5[c]	0.509
Creatinine >100 µmol/l[a] – no. (%)	6 (35.3%)b	1 (5.9%)[b]	0.063	6 (18.8%)c	3 (9.4%)[c]	0.289
Urea week 1 – mmol/l[a]	5.6 ± 3.4[b]	4.9 ± 3.5[b]	0.326	6.1 ± 3.7[c]	6.4 ± 3.2[c]	0.918
Day after birth urea measured[a]	4.3 ± 1.7[d]	3.4 ± 1.7[b]	0.150	3.7 ± 1.8[c]	3.6 ± 1.6[e]	0.472
Inter-twin creatinine difference - µmol/l[a]		22 ± 20			20 ± 23	0.418
Inter-twin urea difference - mmol/l[a]		2.4 ± 2.5			1.9 ± 1.7	0.991

[a]Value given as mean ± SD. [b]Assessed in 17/18 neonates. [c]Assessed in 32/34 neonates. [d]Assessed in 16/18 neonates. [e]Assessed in 31/34 neonates.

Additional information on the hemodynamic and circulatory clinical condition of neonates in the TAPS and control groups is shown in table 4. The heart rate at birth was similar in donors and recipients, but blood pressure was significantly lower in donors compared to recipients. The mean blood pressure at birth in donors and recipients was 37 ± 9 and 43 ± 10 mm Hg, respectively (p = 0.009). Urine output on day 1 was significantly lower in donor twins compared to recipient twins, 2.1 ± 2.0 and 2.4 ± 1.4 ml/kg/h, respectively (p = 0.033). The mean urine output during the first 3 days in donors and recipients in the TAPS group was 3.2 ± 1.6 and 3.6 ± 1.5 ml/kg/h, respectively (p = 0.188).

TABLE 4 Clinical outcome differences between donors and recipients (TAPS group) and smaller and larger twins (control group)

	TAPS group			Control group		
	Donors (N = 52)	Recipients (N = 52)	p-value	Smaller twins (N = 52)	Larger twins (N = 52)	p- value
Birth weight – gr[a]	1434 ± 402	1585 ± 415	0.000	1396 ± 392	1605 ± 428	0.000
SBP at birth – mmHg[b]	53 ± 9[c]	59 ± 12[d]	0.026	50 ± 9[e]	54 ± 14[f]	0.080
DBP at birth – mmHg[b]	28 ± 9[c]	34 ± 10[d]	0.012	26 ± 8[e]	28 ± 11[f]	0.221
MBP at birth – mmHg[b]	37 ± 9[c]	43 ± 10[d]	0.009	34 ± 7[e]	37 ± 13[f]	0.061
HR at birth – bpm[b]	155 ± 12[c]	153 ± 16[d]	0.345	148 ± 19[e]	146 ± 17[f]	0.405
UO Day 1 – ml/kg/h[a]	2.1 ± 2.0[g]	2.4 ± 1.4[h]	0.033	2.1 ± 3.9[i]	2.0 ± 2.1[j]	0.285
UO Day 2 – ml/kg/h[a]	4.1 ± 2.2[g]	4.3 ± 2.1[k]	0.728	4.9 ± 5.1[l]	3.3 ± 1.6[k]	0.177
UO Day 3 – ml/kg/h[a]	3.7 ± 2.1[i]	4.4 ± 2.1[h]	0.072	4.8 ± 4.8[f]	4.3 ± 3.4[k]	0.940
PDA – no. (%)	1 (1.9%)	1 (1.9%)	0.999	2 (3.8%)	2 (3.8%)	0.999
Asphyxia – no (%)[m]	2 (3.8%)	0 (0.0%)	0.500	2 (3.8%)	1 (1.9%)	0.999
Mortality – no. (%)	4 (9.5%)[j]	0 (0.0%)[j]	0.125	1 (1.9%)	0 (0.0%)	1.000

[a]Data given as mean ± SD.
[b]First measured value.
[c]Assessed in 25/52 neonates. [d]Assessed in 26/52 neonates. [e]Assessed in 32/52 neonates. [f]Assessed in 34/52 neonates. [g]Assessed in 41/52 neonates. [h]Assessed in 37/52 neonates. [i]Assessed in 38/52 neonates. [j]Assessed in 42/52 neonates. kAssessed in 40/52 neonates. [l]Assessed in 36/52 neonates.

[m]Asphyxia was defined as the presence of at least three of the following criteria: decelerative cardiotocogram, arterial umbilical cord pH <7.10, 5-minute Apgar score < 5, spontaneous breathing > 5 min after birth or multi organ failure.

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, HR = Heart rate, UO = urine output, PDA = patent ductus arteriosus

Discussion

This is the first study evaluating the short-term renal function in twins with spontaneous or post-laser TAPS. We found that donors have significantly higher creatinine levels compared to recipients during the first week after birth.

Our data suggest that chronic blood loss in donor twins may not only lead to anemia and hypoalbuminemia but may also affect the short-term renal function. Although none of the TAPS donors had signs of severe renal failure requiring treatment during the neonatal period, the focus of this evaluation was mainly based on the short-term outcome. Unfortunately, data on the long-term follow-up of the renal function was often incomplete as most neonates were transferred to general hospitals once intensive care treatment was not required anymore. Whether renal dysfunction may also have long-term consequences,

such as impaired renal function in adult age, requires further investigation.
Various hypotheses may be envisaged to explain the increased rate of short-term renal dysfunction in donor twins. First, increased creatinine levels may reflect a state of chronic hypovolemia due to chronic blood loss ('prerenal hypothesis'). This could also explain the lower blood pressure and lower urine output detected in TAPS donors at birth. However, the absence of increased urea levels and heart rate at birth in donor twins may not fully support the hypothesis of chronic hypovolemia. An alternative hypothesis may be that elevated creatinine levels in donors could result from chronic hypoxia and renal injury due to chronic hypoxia and anemia ('renal hypothesis'). If the renal hypothesis were to be true, the renal injury, which may occur in donor twins, may have permanent effects up to adult age, warranting further long-term investigations. This is in analogy with the 'Brenner hypothesis', which states that retardation of renal development may give rise to an increased postnatal risk for systemic hypertension as well as an enhanced risk of expression of renal disease [9]. Alternatively, short-term renal dysfunction could result from a combination of both prerenal factors (chronic hypovolemia) and renal factors (chronic hypoxia). Lastly, an 'endocrinological' hypothesis could be envisaged, driven by the renin-angiotensin-aldosterone production and resulting in hyperplasia of the juxtaglomerular renin-producing cells in the donor.

In TTTS, a few studies on the postnatal renal function have been performed both in TTTS cohorts treated with fetoscopic laser coagulation as well as in cohorts treated with (serial) amnioreduction. Beck et al. [10] evaluated the long-term outcome of kidney function in 18 twin pairs with TTTS treated by intrauterine laser coagulation and found no evidence of long-term renal function impairment. In a study in 40 TTTS pairs treated with laser at our center, we detected 1 donor with evidence of transient renal failure [11]. The risk of renal failure in donor twins TTTS treated with laser appears thus to be low, probably due to the therapeutic effect of coagulation of the vascular anastomoses and cessation of inter-twin blood flow.

In contrast, most reports in TTTS treated with (serial) amnioreduction show an increased risk of severe renal failure in donor twins. In a study of 33 TTTS twin pairs treated conservatively with amnioreduction at our center, we found severe renal morbidity in 2 (6%) donors. One donor died from terminal renal failure, while the other donor required hemodialysis [12]. Cincotta et al. [13] found that anuria or oliguria were present in 29% (4/14) of the donor twins with TTTS treated with serial amnioreduction. Lenclen et al. [14] also reported an increased incidence of renal failure in TTTS twins treated with amnioreduction (20%, 6/30) but made no distinction between donors and recipients. The etiology and pathology of renal injury in TTTS was evaluated in detail by De Paepe et al. [6] who reviewed the renal pathology in 25 fetal twin pairs. The authors showed that donor twins had a high prevalence of tubular loss, involving both proximal and medullary tubules.

In summary, overall findings in the literature show that the risk of severe renal injury is particularly increased in donors with TTTS treated with amnioreduction. The data in this study suggest that the renal dysfunction in TAPS is less severe and less frequent but still present in both subgroups (spontaneous TAPS and post-laser TAPS). Although TTTS and TAPS are both due to inter-twin blood transfusion, the effect of inter-twin blood transfusion in TTTS are more drastic and cause the rapid development of oligohydramnios and polyhydram-

nios in the donor and recipient, respectively. However, it is important to note that the definitions and criteria of renal failure used in the various studies vary greatly, preventing adequate and accurate comparisons between the different cohorts. For example, more than 30 different definitions for acute kidney injury have been published in the literature [15]. Nevertheless, several recent studies have shown that even a modest rise in creatinine levels is a risk factor for mortality in adults [16]. The data of this study should be interpreted with care due to the retrospective nature of the study and the relatively small sample size. Nevertheless, this study is larger compared to previous reports on renal function in TTTS. Longer and more accurate follow-up of the renal dysfunction would have been more valuable. Unfortunately, this data was often incomplete due to the retrospective nature of this study and the fact that neonates admitted to our tertiary care center are transferred to a general hospital once intensive care treatment is not required anymore. Another potential limitation is that the measurements of creatinine and urea levels were not always determined on the same day. In view of these limitations, our data should be viewed as a starting point for larger studies on renal dysfunction in TAPS or other complicated monochorionic twins.

In conclusion, our data show that donor twins may have an impaired short-term renal function. Our findings add to the understanding of the pathophysiologic characteristics of neonates with TAPS. In view of our findings, we suggest that routine evaluations at birth in neonates with TAPS should not only include hematological measurements but also careful monitoring of renal function. Further investigations should be performed to determine whether renal function may return to normal in donors before discharge and at an older age. Given the rarity of this disease, we have recently set up an international web-based TAPS registry (www.TAPSregistry.org) to evaluate the perinatal mortality and neonatal morbidity associated with TAPS.

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